Uses and Misuses of Genetic Testing in Psychiatry

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* views expressed do not necessarily reflect the policy of the NIH or the Federal Government

Outline

- Potential value of genetic information
- Key questions in evaluating a genetic test
- Currently available tests
- Review of recent ISPG Guidelines
- New challenges for clinical practice, education and research

Potential Uses of Genetic Testing in Psychiatry

- Differential diagnosis
- Prediction of treatment outcomes
  - Response
  - Adverse events
- Identification of high-risk individuals
  - Primary prevention research
  - Preventive strategies

Key Questions

- Can the marker be genotyped *reliably*?
  - Analytic validity
  - Well established for single marker assays, much less certain for assays based on NGS
- How *valid* is the association with disease?
  - Sample size
  - Replication
  - Functional?
- Does the test result have any *clinical utility*?
  - Effect size
  - Unique information?
  - Do alternative treatments/diagnoses exist?

Genetic Testing is Already Here in Psychiatry

- Commercial panels marketed to psychiatrists and psychologists, e.g.,
  - Recurrent CNV's associated with developmental disorders
  - Cytochrome p450 markers
  - SERT LPR
- Direct marketing to patients and their relatives
  - SNP arrays

Kinds of Genetic Variation Currently Subject to Testing

- Common risk alleles
  - e.g., APOE4, GWAS hits
- CNV
  - Recurrent
  - De novo
- Rarer risk alleles (eg PKU)
- Expanded repeats (eg HT)
- (Traditional cytogenetics)

Available Through Clinicians

- Long established tests of causal genetic and chromosomal lesions, e.g.,
  - Phenylketonuria
  - Huntington disease
  - Fragile X syndrome
- More recently developed tests for genetic risk factors that are not causal
  - APOE (Alzheimer disease)
  - copy number variants (ASD, schizophrenia)
  - CYP450 (drug metabolism)

Available to Consumers

- Single nucleotide arrays
  - Health implications based on GWAS findings
  - Also some rare Mendelian disorders, incl BRCA
  - APOE
  - Marketing of health claims tightly regulated or prohibited in some countries
- Sequence (exome, whole genome)
  - "Personal genomes"
- Other products

NeuroMark

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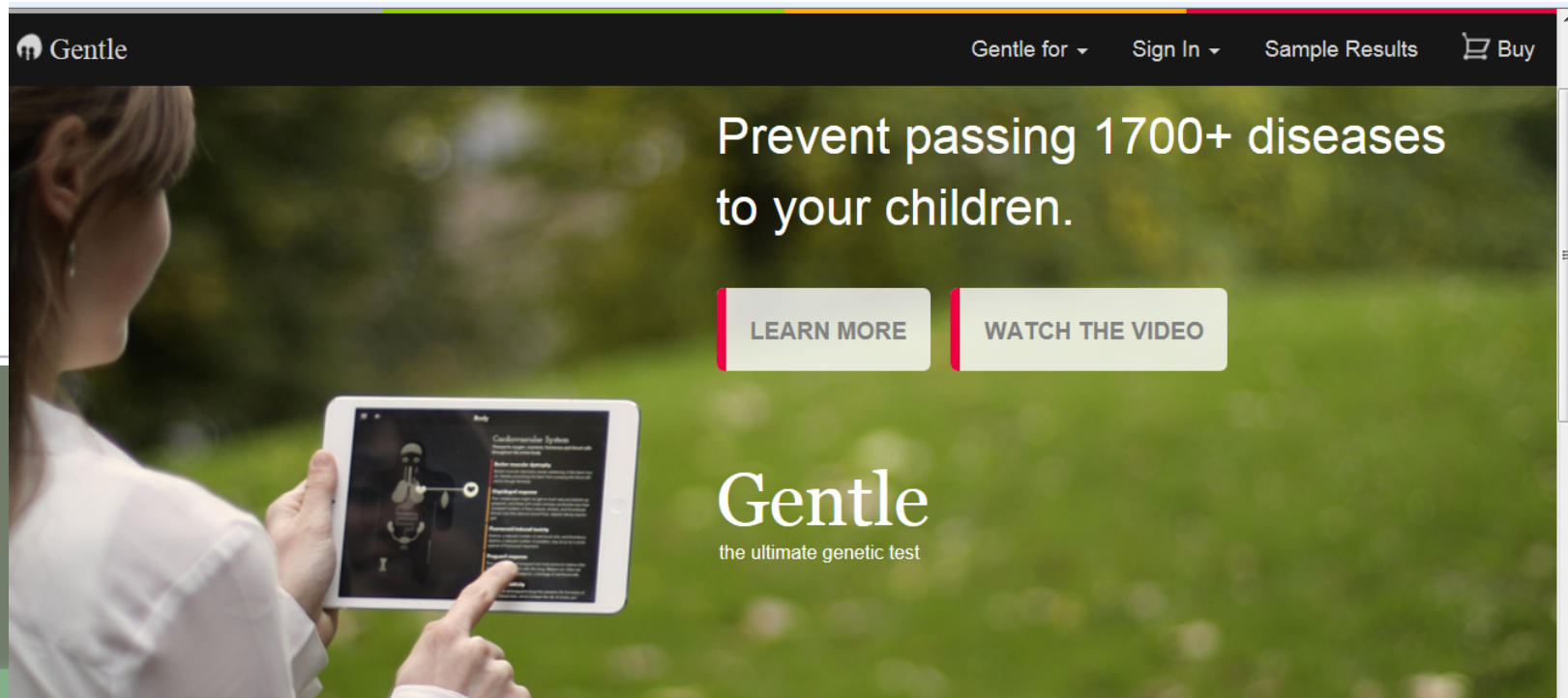
1866: Gregor Mendel discovers the laws of inheritance.



Informed Consent

- Fundamental principle
- Respects individual autonomy
- Objective presentation of risks & benefits
- Routine for surgery, rare for psychiatry
- Recommended prior to clinical genetic testing

Single Gene Testing

- Psychiatric disorders are not monogenic
- Single genes have a very small impact on individual risk
- Not clear whether large sets of genes, tested together, could have a larger impact
  - Published studies suggest AUCs in the 55-65% range, well below usual thresholds of clinical utility
  - Interaction with other factors (eg, family history) has so far been little studied

CNV Testing

- Small chromosomal deletions and duplications are more common in autism, schizophrenia, and (maybe) bipolar disorder than in healthy controls
- Individually rare, taken together CNVs may account for ~5% of cases
- Carriers may be at risk for other medical conditions when the CNV causes a contiguous gene syndrome

Pharmacogenetic Tests without Evidence of Clinical Utility in Psychiatry

- CYP450
  - Valid association with drug metabolism
  - No evidence of clinical utility
  - More study is needed of treatment-resistant depression
- Serotonin Transporter
  - LPR polymorphism influences serotonin re-uptake
  - Weak associations with a broad range of symptoms
- Others: MTFHR, HTR2A, BDNF

Some Promising Pharmacogenetic Tests

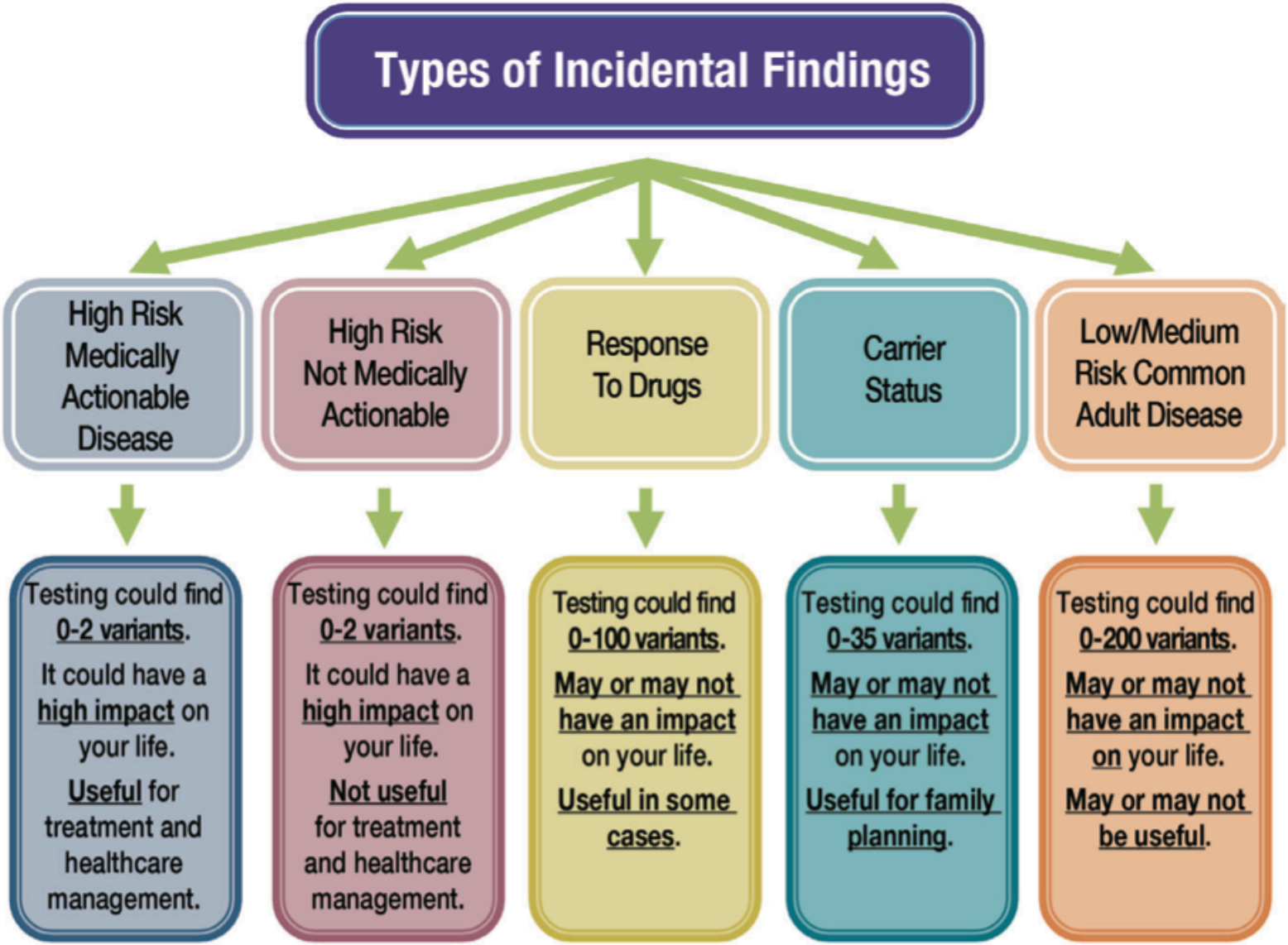
- HLA testing prior to carbamazepine may decrease risk of rare adverse drug events
  - HLA-B*1502 in Asians
  - HLA-A*3101in most people
- Other tests, eg, for lithium response, await replication

Genetic Counseling

- Ideally used before testing, in order to evaluate its potential and anticipate results
- Useful for understanding results and secondary findings
- Challenges in integrating traditional genetic counseling and psychiatric care
  - Need for both genetic and mental health expertise

Incidental and Secondary Findings

- Can arise with any genome-wide test
- May highlight unanticipated findings of health significance
- Require a plan for identifying, reporting, and counseling
- ACMG guidelines are a good starting point



http://www.research.chop.edu/programs/pediseq/index.php/discover/healthcare-providers/results-2.html#Incidental

Education of Clinicians and Patients

- Many clinicians do not feel well informed about genetics
  - Especially true for psychiatrists?
  - Genetic counseling is not the same as mental health counseling
  - Indications for genetic testing are not clear
- Patients often have little understanding of genetics
  - Overestimate importance of genetic findings
  - Concept of "genetic risk factor" may be misunderstood

Need for More Research

- Clinical validity of most gene tests remains uncertain
  - Need for replication in large samples
- Clinically valid gene tests may still lack clinical utility
  - Effect sizes may be small
  - Gene test may provide little unique information
- Can genetic testing do harm?
  - Little is known about how psychiatric patients deal with genetic results with potentially serious health implications

ISPG Genetic Testing Task Forces

- 2008-2009
  - Broadly recommended against all testing (except PKU, Fragile X, and HD)
- 2012-2013
  - Goal was to update recommendations in light of recent research
  - Draft recommendations *not* adopted by the Board
- 2013-2014
  - "Crowd-sourced" the work to a large group of ISPG members
  - Series of conference calls aiming at broad consensus
  - Final recommendations recently adopted by the Board and posted on ISPG website (www.ispg.net)

ISPG Summary Recommendations

1. Genetic tests should only be carried out if patients have given informed consent.
2. For major adulthood psychiatric disorders, single genetic variants are not sufficient. There are no genetic tests that can establish a diagnosis or predict individual risk.
3. Identification of certain copy number variants (CNVs) in individuals with autism spectrum disorders or schizophrenia may help diagnose rare conditions with important medical and psychiatric implications for patients and may inform family counseling.
4. Clinicians should consider evolving pharmacogenetic testing recommendations in treatment decisions.
5. Evidence remains inconclusive as to the possible clinical utility of CYP450 testing, but more research is needed.

ISPG Summary Recommendations [cont]

6. All genetic tests with health implications should be accompanied by professional genetic counseling. For patients with psychiatric illness, or for tests that relate to psychiatric conditions, counselors should possess clinical expertise in mental health.
7. In genome-wide testing, the possibility of incidental or secondary findings must be clearly communicated. Procedures for dealing with such findings should be made explicit.
8. We advocate programs to educate mental health professionals in genetic medicine, safeguard the privacy of individuals' genetic testing results, and reduce stigma in the community.
9. Expanded research efforts are needed to clarify the role of genetic testing in psychiatry.

Conclusions

- Genetic testing is becoming a reality in psychiatry
- Clinical utility of psychiatric genetic tests is generally limited or unknown
- Use of certain genetic tests in specific situations may be warranted
- Need for more genetic education of clinicians and patients
- Need for additional research

ISPG Genetic Testing Taskforce

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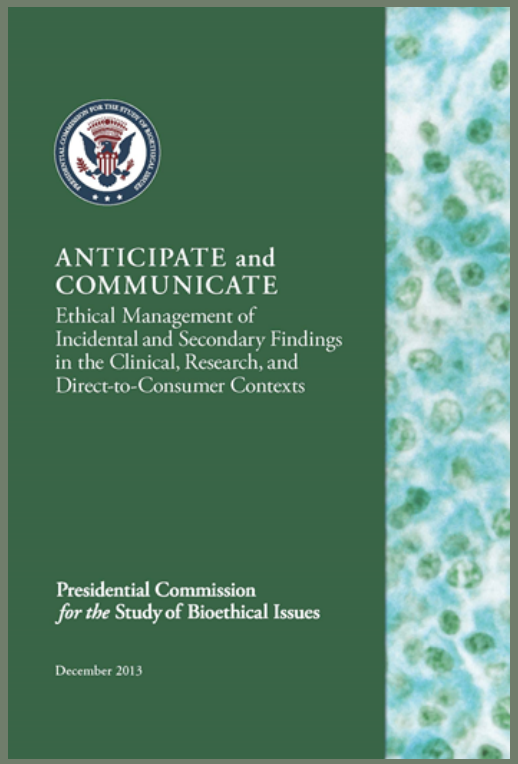
Advantages of DTC Testing

- **Autonomy**: Respects the desire to learn about one's own genetic makeup
  - Ancestry networks
  - Familial traits
  - Gene-based social networks
  - Health risks
- **Equality**: Equalizes data access between clinicians and patients
- **Enlightenment**: May heighten awareness and understanding of genetics among non-specialists

Disadvantages of DTC Testing

- **Exploitation**: DTC companies have a profit motive that may conflict with consumers' best interests
- **Loss of context**: Health related risks cannot be judged outside the context of family history and non-genetic risk factors
- **False knowledge**: Most genetic markers in psychiatry represent weak statistical risk factors, with poor specificity and little predictive value

Presidential Commission



Five Broad Recommendations

1. Inform potential recipients . . . about the possibility of incidental or secondary findings, and if and how those findings will be disclosed…
2. Develop guidelines that categorize findings likely to arise from each diagnostic modality, and best practices for managing them.
3. Fund research to keep abreast of the rapidly evolving types and frequency of findings; potential costs, benefits, and harms; and … preferences about incidental and secondary findings.
4. Prepare materials and enhance education of all stakeholders . . . about the ethical, practical, and legal considerations raised by incidental and secondary findings.
5. [Provide] access to information and the guidance needed to make informed choices about what tests to undergo, what kind of information to seek, and what to do with information once received.